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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,828	04/09/2004	Hector F. DeLuca	1256-00949	1399

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EXAMINER
BADIO, BARBARA P

ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,828	DELUCA ET AL.	
	Examiner	Art Unit	
	Barbara P. Badio	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 22-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 22-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Final Office Action on the Merits of a RCE

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Double Patenting

2. The rejection of claims 1-17 and 22-71 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of U.S. Patent Nos. 5,843,928; 6,114,317; 6,392,071; 6,440,953; 6,482,812; 6,537,981; 6,566,352; 6,579,861; 6,627,622; 6,696,431; 6,774,251; 6,806,262; 6,887,860; 6,894,037; 6,992,074; 7,053,075; 7,094,774; 7,115,594; 7,141,558; 7,208,484; 7,214,670; 7,214,671; 7,232,810; 7,241,747; 7,241,748; 7,241,909; 7,244,719, 7,300,925 and 7,511,030 (previously 11/351,874)in view of Bishop et al. (US 5,972,917) or Deluca et al. (WO 96/16035) is maintained.

Applicant argues (a) although the data referred to by Applicant is found in a number of different prior art references, all the data was obtained via the same techniques and (b) the presently claimed compound have significantly different calcemic activities from the prior art compound. According to applicant, the closest prior art compound is (20S)-2-methylene-19-nor-1α,25-dihydroxyvitamin D_3. Applicant's argument was considered but not persuasive for the following reasons.

The examiner maintains that the comparison made by applicant is not a true side-by side comparison. Although, the data obtained by the references was obtained

by the same procedures, it does not follow that it is a true side-by-side comparison. The skilled artisan in the art would know that two laboratories utilizing the same assay can obtain differ results. Additionally, the workup/preparation is as important as the assay utilized. For example, section 00137 of the present specification described the experiment as:

> **[00137]** Weanling, male Sprague-Dawley rats were purchased from Harlan. Upon receipt, the animals were identified by individual tail marks and fed a calcium containing (0.47%) diet (Suda et al., Purified Rodent Diet-Diet 11; Appendix A) for one week before switching to the same diet devoid of calcium (0.02%). Water and a purified rodent diet (Diet 11; Appendix A) containing either 0.47% or 0.02% calcium and 0.3% phosphorus were provided ad libitum. Animals were fed the purified diet containing 0.47% calcium for the first week and then the 0.02% calcium containing diet for the next three weeks of the study. The rats were then fed 0.47% calcium containing diet for one week before switching back to 0.02% calcium containing diet for the remainder of the study. During the second week back on 0.02% calcium containing diet, the animals were tail-bled (baseline serum calcium) and then dose administration was initiated. All doses were administered intraperitoneally in 100 microliters of propylene glycol. Four consecutive doses were given approximately 24 hours apart. Twenty-four hours after the last dose, blood was collected from the tail artery of each experimental animal. The blood was allowed to coagulate at room temperature and then centrifuged at 3000 x g for 15 minutes. The serum was transferred to a polypropylene tube and stored frozen at -20°C. The level of calcium was determined by diluting the serum into 0.1% lanthum chloride and measuring the absorbance on an atomic absorption spectrophotometer (Perkin Elmer Model 3110, Shelton, CT).

whereas the description in '928, col. 16, line 57 – col. 17, line 4 is as follow:

Male weanling rats were obtained from Sprague Dawley Co. (Indianapolis, Ind.) and fed a 0.47% calcium, 0.3% phosphorus vitamin D-deficient diet for 1 week and then given the same diet containing 0.02% calcium, 0.3% phosphorus for 2 weeks. During the last week they were given the indicated dose of compound by intraperitoneal injection in 0.1 ml 95% propylene glycol and 5% ethanol each day for 7 days. The control animals received only the 0.1 ml of 95% propylene glycol, 5% ethanol. Twenty-four hours after the last dose, the rats were sacrificed and intestinal calcium transport was determined by everted sac technique as previously described and serum calcium determined by atomic absorption spectrometry on a model 3110 Perkin Elmer instrument (Norwalk, Conn.). There were 5 rats per group and the values represent mean ±SEM.

. There are a number of differences between the two experiments. For example, (a) **the diet of the animals**: In the '928 patent, the animals were fed (i) 0.47% calcium, 0.3% phosphorus vitamin D-deficient diet for 1 week and (ii) two weeks of 0.02% calcium, 0.3% phosphorus vitamin D deficient diet whereas in the present specification, the animals were fed (i) a 0.47% calcium containing diet for one week and (ii) three weeks of a 0.02% calcium containing diet; (b) **the vehicle in which the compound was dissolved**: In '928, a 95% propylene glycol/5% ethanol solvent system was utilized whereas in the present specification, *propylene glycol* was utilized alone; (c) **the duration of administration**: In '928, administration was daily for 7 days whereas in the present specification, it was 4 consecutive doses approximately 24 hours apart and (d) **the handling of the blood obtained for the assay**: Unlike the '928, the present specification states the blood

obtained was allowed to coagulate, was centrifuged before determining the calcium level. Any or all of the above could affect the outcome of the data.

Applicant also argues the presently claimed compound has significantly different calcemic activities from the prior art compound, i.e., the presently claimed compound has selective activity on intestinal calcium transport, but not on bone, whereas the prior art compound has selective activity on stimulating bone mobilization, but not on intestinal calcium transport. Applicant's argument was based on the data obtained from different references. As noted above, the comparison is not a true side-by-side comparison.

Additionally, as noted by the present specification 18,19-dinor vitamin D compounds are known in the art (see page 2, section 0006 of the present specification). US patent No. 5,843,927, noted by the present specification, teaches 18,19-dinor vitamin D derivatives have preferential activity on intestinal calcium transport with reduced bone calcium mobilization:

The above novel compounds exhibit a desired, and highly advantageous, pattern of biological activity. These compounds are characterized by a marked intestinal calcium transport activity, as compared to that of 1α, 25-dihydroxyvitamin D_3, while exhibiting lower activity than 1α,25-dihydroxyvitamin D_3 in their ability to mobilize calcium from bone. Hence, these compounds are highly specific in their calcemic activity. Their preferential activity on intestinal calcium transport and reduced calcium mobilizing activity in bone allows the in vivo administration of these compounds for the treatment of metabolic bone diseases where bone loss is a major concern. Because of their preferential calcemic activity, these compounds would be preferred therapeutic agents for the treatment of diseases where bone formation is desired, such as osteoporosis, osteomalacia and renal osteodystrophy.

(see col. 3, lines 24-38).

Thus, the skilled artisan would have the reasonable expectation that the corresponding 18,19-dinor derivatives of the cited patents would have similar properties as taught by the prior art.

However, even if one agrees with the validity of the comparison, it is not commensurate in scope. For example, the art teaches:

The introduction of a methylene group to the 2-position of the 24(S) and 24(R) isomers of 19-nor-1,25-$(OH)_2D_2$ increased binding to the porcine 5 intestinal vitamin D receptor as compared to 1α,25-dihydroxyvitamin D_3. These compounds bound better to the porcine receptor as compared to the standard 1,25-$(OH)_2D_3$ (FIG. 1). It might be expected from these results that these compounds would have increased biological activity in stimulating intestinal calcium transport and bone calcium mobilization. Surprisingly, however, the 2-methylene and 24-epi substitutions produced highly selective analogs with their primary action on stimulating intestinal calcium transport.

(see for example, '**810**, col. 14, line 57 - col. 15, line 2);

The binding of the 25-methyl derivative TMM to the recombinant rat vitamin D receptor illustrates that TMM binds one-tenth as well to the vitamin D receptor as the native hormone, 1,25-$(OH)_2D_3$. This is surprising because TMM lacks a 25-hydroxyl group. However, TMM, when tested in HL-60 differentiation, revealed activity essentially equal to that of 1,25-$(OH)_2D_3$. Thus, TMM is very potent even without a 25-hydroxyl group. Of great interest is the in vivo data obtained in CD-1 mice. The data on animals following a single dose of the compound at the indicated levels showed that TMM had very little bone calcium

> mobilization activity. Bone calcium mobilization (serum calcium level) was minimal even up to 13.5 micrograms of TMM/kg body weight. Thus, its activity not only fell far below 2-methylene-19-nor-20(S)-1α, 25-$(OH)_2D_3$ or 2MD but also below that of the native hormone, 1,25-$(OH)_2D_3$. Of considerable interest, however, is that TMM had a very strong effect on intestinal calcium absorption. The activity of TMM on intestinal calcium absorption is 10 times that of 1,25-$(OH)_2D_3$ which in previous work was shown to have about the same activity as 2-methylene-19-nor-20(S)-1α, 25-$(OH)_2D_3$. Thus, TMM shows selectivity for activity on the intestine, where utilization of environmental calcium is highly desirable without associated bone calcium mobilization. It could be used as a maintenance vitamin D compound in patients where bone loss due to bone mobilization is not desired. Such a circumstance could be any form of osteoporosis. The activity of TMM in causing cellular differentiation and suppression of HL-60 cell growth is also consistent with its use in the treatment of malignant disease or in the treatment of psoriasis, a hyperproliferation of keratinocyte disease of skin.

(see for example, '**037**, col. 12, line 57 – col. 13, line 21). Based on said teachings and the knowledge in the art of 18,19-dinor vitamin D compounds, the skilled artisan would have the reasonable expectation that the 18,19-dinor derivatives of the cited patents would show selective activity on calcium mobilization.

Lastly, in response to the two other issues cited by Applicant, the Examiner notes (a) that the 18-nor and not the 18,19-dinor compound was argued as having little, if any, calcemic activity and (b) the previous Office Action stated that "*the introduction of 2-methylene group changes the character of the hydroxyl groups which are crucial for the biological activity of vitamin D compounds*" and not that the introduction of a 2-methylene group would result in compounds with little, if any, calcemic activity.

For these reasons and those given in the previous Office Action, the rejection of claims 1-17 and 22-71 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of U.S. Patent Nos. 5,843,928; 6,114,317; 6,392,071; 6,440,953; 6,482,812; 6,537,981; 6,566,352; 6,579,861; 6,627,622; 6,696,431; 6,774,251; 6,806,262; 6,887,860; 6,894,037; 6,992,074; 7,053,075; 7,094,774; 7,115,594; 7,141,558; 7,208,484; 7,214,670; 7,214,671; 7,232,810; 7,241,747; 7,241,748; 7,241,909; 7,244,719, 7,300,925 and 7,511,030 (previously 11/351,874) in view of Bishop et al. (US 5,972,917) or Deluca et al. (WO 96/16035) is maintained.

3. The provisional rejection of claims 1-17 and 22-71 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application Nos. Nos. 10/997,698; 11/697,414; 11/697,434 and 11/697,436 in view of Bishop et al. (US 5,972,917) or (Deluca et al., WO 96/16035) is maintained.

It is noted that Application No. 11/351,874 previously cited is now US Patent No. 7,511,030 and, thus, the provisional rejection is removed and the instant claims are rejected over the above mentioned patent (see paragraph 2 above).

For the reasons given above in #2 and those given in the previous Office Actions, the provisional rejection of claims 1-17 and 22-71 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending

Application Nos. Nos. 10/997,698; 11/351,874; 11/697,414; 11/697,434 and 11/697,436 in view of Bishop et al. (US 5,972,917) or (Deluca et al., WO 96/16035) is maintained.

Conclusion

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Telephone Inquiry

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Barbara P. Badio whose telephone number is 571-272-0609. The examiner can normally be reached on M-F from 6:30am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Barbara P. Badio/
Primary Examiner, Art Unit 1612